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Meta-regression insights for optimizing accelerated neuromodulation protocols in major depression

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ABSTRACT

Accelerated neuromodulation, which involves multiple daily sessions of repetitive transcranial magnetic stimulation (rTMS), is increasingly recognized as a time-efficient and clinically effective treatment for major depressive episodes, including treatment-resistant and bipolar depression. Given the considerable variability in stimulation parameters and therapeutic outcomes, this study aims to provide preliminary insights to optimize accelerated excitatory rTMS protocols for enhanced clinical efficacy.

We performed a meta-regression analysis including controlled and uncontrolled trials reporting the effect of high-frequency prefrontal cortex accelerated rTMS (arTMS) and intermittent Theta Burst Stimulation (aiTBS) on depression response rate in patients diagnosed with major depressive disorder, treatment-resistant depression and bipolar depression (both men and women, all ages).

The systematic search identified 25 arTMS/aiTBS interventions in depression studies with 5 or more participants, totaling 810 participants and 722 stimulation sessions.

Meta-regression analysis revealed a significant dose–response relationship in clinical outcomes. Both a higher number of pulses and a greater total number of sessions (i.e., more than 20) were associated with enhanced antidepressant effects. Additionally, longer intersession intervals (≥50 min) appeared to positively influence treatment effectiveness. No significant differences emerged between stimulation modalities (iTBS vs. arTMS) or methods of target localization.

Despite some limitations, these findings provide preliminary evidence of the significant impact that parameter settings in accelerated rTMS protocols have on clinical outcomes, offering valuable guidance for the future optimization of neuromodulation strategies in the treatment of depression.

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1. Introduction

Depression carries significant medical and social burdens, driving extensive global research efforts aimed at identifying effective therapeutic approaches. The limited response to first-line antidepressant treatments, along with the rising prevalence of treatment-resistant depression (TRD), has spurred the development of non-invasive neuromodulation techniques. Among these, repetitive transcranial magnetic stimulation (rTMS)—a method that modulates cortical excitability via magnetic pulses—has emerged as a particularly promising intervention (Lisanby, 2024).

The introduction of accelerated rTMS (arTMS) protocols—defined as the administration of ≥2 sessions per day—has shown considerable promise in advancing the clinical utility of neuromodulation for the treatment of depression (Chen et al., 2023). Compared to standard protocols delivering one session per day, arTMS has demonstrated comparable efficacy (Shi et al., 2024; Pettorruso et al., 2023), with an average response rate of 42.4 % (Caulfield et al., 2022). Nonetheless, the considerable variability in reported outcomes—ranging from 19.4 % to 90.5 %—leaves open the critical question of which specific protocol parameters most significantly determine clinical efficacy.

Although it is well established that neuromodulation can be administered through highly heterogeneous protocols, accelerated approaches introduce additional layers of variability. Standard rTMS protocols may differ in several key parameters: total dose (defined by the cumulative number of pulses or sessions); type of stimulation (single-pulse trains in conventional rTMS vs. triplet-pulse trains in Theta Burst Stimulation, TBS); stimulation frequency (in rTMS: low frequency <5 Hz, typically inhibitory, vs. high frequency >5 Hz, typically excitatory; in TBS: continuous [cTBS], inhibitory, or intermittent [iTBS], excitatory); stimulation intensity (expressed as a percentage of the resting motor threshold, RMT); and methods of target localization (using craniometric measurements, structural imaging, or functional imaging). Accelerated protocols, however, must also define additional parameters, including the number of sessions delivered per day (ranging from 2 to as many as 10), the total number of treatment days required to complete the protocol, and the intersession interval, which can range from 15 min to 12 h (Caulfield et al., 2022).

Caulfield et al. (2022) recently conducted a qualitative analysis of various arTMS/aiTBS parameters, highlighting the potential impact of protocol heterogeneity on clinical outcomes. However, a quantitative approach is crucial to strengthen our understanding of the underlying mechanisms and to identify the most effective implementation strategies—thereby supporting the broader integration of arTMS into clinical practice.

To address this need and inform the development of future protocols grounded in stronger empirical evidence, we performed meta-regression analyses on data from both controlled and uncontrolled trials reporting the effects of accelerated high-frequency rTMS or intermittent TBS parameters on response rates in patients with depressive disorders. Owing to differences in their hypothesized mechanisms, we focused solely on excitatory protocols—which constitute the majority of current arTMS interventions—to investigate a potential linear effect. Expanding the analysis to inhibitory and combined protocols, and defining their respective efficacy domains, was deferred to future studies.

2. Methods

2.1. Protocol

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework. The study protocol was pre-registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024552199).

2.2. Literature search and eligibility criteria

We performed a meta-regression analysis of data from controlled and uncontrolled trials reporting the effects of accelerated protocols of high-frequency rTMS or iTBS on depression response rate in patients diagnosed with major depressive disorder (MDD), treatment-resistant depression (TRD) and bipolar depression (BD) (both men and women, all ages).

We included only studies of TMS interventions targeting the prefrontal cortex, specifically the dorsolateral and dorsomedial regions. Studies with less than 5 participants and studies not reporting the number of responders were excluded. Only studies assessing depressive symptomatology with validated depression rating scale (i.e., standardized psychometric instruments) were included. Studies combining different intervention protocols (e.g., excitatory and inhibitory) were excluded from the analysis.

Articles published before May 22, 2024 were identified using PubMed. Key words used included a combination of *accelerated* or *intensive* and *transcranial magnetic stimulation* or *theta burst* along with *depress** (abbreviations and synonyms included). Supplementary searches of relevant systematic reviews were performed manually.

Two reviewers screened titles/abstracts and full texts. Discrepancies were resolved by consensus with a third reviewer.

2.3. Outcomes and data extraction

Primary outcome: depression response rate (RR), defined as the proportion of responders (i.e., individuals showing a ≥50 % reduction in depressive symptoms) within the total sample. RRs were collected immediately after treatment (within one week of the final session).

Secondary outcome: depression remission rate (RmR), defined as the proportion of remitters, namely individuals whose symptoms were reduced to a level no longer considered clinically significant, based on a cutoff score on standardized rating scales. As for RRs, RmRs were collected immediately after treatment.

In addition to the outcomes, two independent authors extracted the following data from eligible studies: i) Bibliographic identifiers; ii) Population: number of accelerated rTMS participants, diagnosis, mean age at baseline, proportion of males; iii) Study design; iv) Intervention: stimulation location, targeting method, TMS intensity (% motor threshold), TMS frequency (Hz), train duration (seconds), intertrain interval (seconds), number of trains per session, total pulses per session, number of sessions per day, intersession interval (minutes), number of treatment days, total number of sessions, tapering, neuronavigation, total pulses, assessment instrument/tool, assessment timing.

Two reviewers extracted all data. Discrepancies were resolved by consensus with a third reviewer.

2.4. Data analysis

Average RR and corresponding 95 % Confidence Interval (CI) were calculated using a random-effects meta-analysis including both controlled and uncontrolled studies (effect size index: event rate).

The extent to which study-level variables explained outcome heterogeneity was investigated by fitting multivariable meta-regression models (random-effects [MM], Z-distribution).

The first model (*dosing factor*) included the following variables: type of stimulation (rTMS vs iTBS), method of target localization (neuronavigated or not), and total pulses (number in thousands).

To provide guidance on dose distribution (*timing factor*), we have developed a model that considers how sessions are differently "concentrated" across days (total sessions = sessions/day × number of days) and temporally spaced. This model thus included the following variables: type of stimulation (rTMS vs iTBS), pulses per session (number), number of sessions, number of days, and intersession interval (in minutes).

The secondary outcome (short-term RmR) was included in a sensitivity analysis to explore whether the main findings were observable using this alternative parameter. Given that patients with BD may respond differently to neuromodulation interventions (Gama-Chonlon et al., 2022), an additional sensitivity analysis was performed excluding studies that included participants diagnosed with BD.

A subgroup analysis was conducted comparing studies using short versus long intersession intervals to explore the effect of intersession interval duration on outcomes. The categorization of intervals was derived from the distribution of observed durations across studies (sample median: 50 min). Short intervals were defined as 10–30 min and long intervals as ≥50 min. No studies reported intervals between 30 and 50 min.

All analyses were conducted using Comprehensive Meta-Analysis (Version 4). Risk of bias was evaluated using RoB 2 (Sterne et al., 2019).

3. Results

The PubMed search returned 167 results; among these, 49 were not relevant to the subject reading title and abstract, and 23 were non-original articles. Of the 95 full-text articles assessed for eligibility, 68 did not match the inclusion criteria for our review, and 4 were not available. The manual search identified an additional article that met the inclusion criteria. Finally, 24 articles were included in the final review (see eFig. 1 for the flow diagram of the study selection process). The final sample consisted of 25 arTMS/aiTBS interventions with 5 or more participants, totaling 810 participants and 722 stimulation sessions (see Table 1 for characteristics of the included studies). Risk of bias assessment indicated that 15 studies were at high risk, 6 had some concerns, and 3 were at low risk (eFig. 2).

The depression response rate ranged from 19.4 % to 90.5 % across studies. On average, 52.2 % (95 % CI: 44.2–60.0 %) of participants achieved a ≥50 % reduction in depressive symptoms (response) following the intervention (random-effects meta-analysis), with substantial/considerable heterogeneity (I^2 = 74.8 %). In the 24 studies assessing remission, on average 32.5 % (95 % CI: 24.9–41.2 %) of participants experienced a reduction in depressive symptoms to a level no longer considered clinically significant.

The extent to which study-level variables could explain heterogeneity in RR was explored by fitting random-effects multivariable meta-regression models. The analyses highlight the central importance of the 'total dose' of TMS pulses in accelerated neuromodulation (*dosing factor*; Fig. 1 and Table 2). Results remained consistent when studies including BP patients were excluded (eTable 1a). Moreover, only the total number of TMS pulses was significantly associated with the depression response rate, while demographic and clinical characteristics of the patients showed no significant effects when controlling for total pulses (eTable 2).

Additionally, we developed a model that considers how the dose is distributed (*timing factor*; Fig. 2). Results show that increasing the total number of sessions ($p < 0.01$; Fig. 2a), rather than the number of pulses per session ($p > 0.05$; Fig. 2b), appears to be more beneficial. Furthermore, maintaining adequate intersession intervals seems to be crucial ($p < 0.05$; Fig. 2c). Long intervals (≥50 min) appear to significantly improve the efficacy of arTMS protocols (subgroup analysis - test of interaction: Q = 12.581, df = 1, p < 0.001; eTable 3). Notably, concentrating the dose over a few days does not seem to negatively impact the efficacy ($p > 0.05$; Fig. 2d), confirming the idea that, with adequate intersession intervals, the activation of neuroplastic phenomena by arTMS protocols is not negatively affected by concentrating the dose over fewer days. When studies including BP patients were excluded, results remained consistent, showing a significant effect of both the total number of sessions and the intersession interval on depression RR (eTable 1b).

When applied to the secondary outcome (RmR), the multivariable meta-regression models revealed a less consistent pattern compared to the findings for RR. While the total dose of TMS pulses remained a key determinant of remission (eTable 4a), variations in the intersession interval no longer showed a significant effect, and only a non-significant trend emerged for the total number of sessions (p = 0.07; eTable 4b). Weaker associations with some stimulation parameters were anticipated, given the more limited clinical relevance of acute remission compared to short-term response rate.

4. Discussion

Given the number of available studies (n = 24) and the substantial heterogeneity observed in both stimulation parameters and clinical outcomes (I^2 = 74.8 %), we conducted a quantitative meta-regression analysis. Although the method carries inherent limitations—such as variability in study design, sample size, and outcome measures—and further research is needed to validate these findings, the analysis offers preliminary guidance for researchers and clinicians seeking to select protocol parameters most likely to enhance therapeutic efficacy.

The analyses highlight the central importance of the total dose of TMS pulses even in accelerated neuromodulation (Fig. 1), confirming for the first time through a quantitative approach what was recently proposed (Lefaucheur et al., 2025). Several meta-analyses on standard rTMS (Hsu et al., 2024) have demonstrated a dose–response relationship, with treatment effects increasing with dose up to a saturation point, beyond which no further benefit is observed (Yu et al., 2024). This study provides the first replication of what was previously observed with standard rTMS, offering clear guidance for developing more efficient accelerated protocols. It is intriguing that this notion—beyond being interpretable similarly to pharmacological interventions (i.e., more stimuli, more effect)—may also hold meaning in terms of the likelihood of engaging the target when considered within a brain-state dependent stimulation framework (i.e., more stimuli, greater probability of encountering the brain in a receptive state; Sack et al., 2024; Makkinayeri et al., 2025).

Furthermore, our analysis suggests that neither the type of stimulation (rTMS vs. iTBS) nor the method of target localization (neuronavigated vs. non-neuronavigated) significantly contributes to the variance in treatment response (Table 2). This observation aligns with emerging evidence indicating that advanced fMRI-based targeting methods account for only a limited portion of the variability in neuromodulation outcomes (Elbau et al., 2023), in line with the hypothesis that non-neuronavigated protocols—by engaging broader, functionally relevant neural networks—may enhance clinical efficacy in the treatment of depressive disorders (Briley et al., 2024). While this finding should be interpreted with caution, its replication in larger, prospective studies could have important implications for how healthcare systems prioritize and allocate resources for the clinical application of neuromodulation therapies (Millet et al., 2025).

In examining the temporal distribution of the dose, we developed a model that incorporates parameters specific to accelerated protocols (Fig. 2). An identical total number of sessions can be delivered with varying levels of temporal compression, depending on the number of sessions per day and the total number of treatment days. Assuming that dose distribution follows "iso-sessions" curves (total sessions = sessions per day × number of days), specifying any two of these three parameters allows for the unique determination of a specific temporal dosing configuration. The interval between sessions (i.e., intersession interval) may influence the efficacy of neuromodulatory interventions, independently of the total pulse dose. Notably, our findings suggests that the number of sessions—rather than the number of pulses per session—is the primary factor driving increased efficacy in accelerated protocols. Moreover, delivering treatment over a shorter overall duration does not appear to compromise clinical outcomes.

Our meta-regression insights support the hypothesis that the neuroplastic mechanisms engaged by arTMS are not compromised by a condensed treatment schedule, provided that adequate intersession

Table 1
Characteristics of depression studies employing arTMS/iTBS.

First author, year	Diagnosis	Age (mean)	Sex (% M)	TMS Type	TMS Freq. (Hz)	TMS Intensity (% MT)	Neuronav. (Y/N)	Intersession Interval (min)	Pulses per session (n)	Sessions per day (n)	Treatm duration (days)	Total sessions (n)	Total pulses (n)	Sample size	RR
Baeken et al., 2013	TRD	49.3	38.0	arTMS	20	110	N	17.5*	1560	5	4	20	31200	20	0.350
Barnes et al., 2023	MDD	46.4	25.0	arTMS	10	120	N	240£	5625	2	10	20	112500	109	0.596
Blumberger et al., 2021	MDD	40.7	33.9	iTBS	–	120	Y	60	600	2	30	60	36000	88	0.443
Bröcker et al., 2019	MDD/BD	40.7	22.2	iTBS	–	80	N	20	1782	2.5	8	20	35640	9	0.556
Bulteau et al., 2019	BD	52.7	41.7	iTBS	–	80	Y	180	990	2	15	30	29700	12	0.750
Cole et al., 2020	TRD	44.9	42.8	iTBS	–	90	Y	50	1800	10	5	50	90000	21	0.905
Cole et al., 2022	TRD	49.0	64.0	iTBS	–	90	Y	50	1800	10	5	50	90000	14	0.714
Dardenne et al., 2018	MDD	73.9	0.0	arTMS	20	110	N	15	1560	5	4	20	31200	10	0.400
Desbeaumes Jodoin, 2019	MDD	57.4	49.0	arTMS	20	110	N	90	3000	2	10	20	60000	73	0.452
Duprat et al., 2016	TRD	41.7	29.8	iTBS	–	110	Y	15	1620	5	4	20	32400	47	0.277
Filipčić et al., 2021a	MDD	52.0	44.0	arTMS	18	120	N	560#	1980	2	10	20	39600	16	0.625
Filipčić et al., 2021b	MDD	56.0	50.0	arTMS	18	120	N	560#	1980	2	15	30	59400	12	0.833
Fitzgerald et al., 2018	MDD	48.2	43.1	arTMS	10	120	N	22.5**	3500	3	6	18	63000	59	0.203
Fitzgerald et al., 2020	MDD	44.0	47.2	iTBS	–	120	N	15	600	3	7	21	12600	36	0.278
Holtzheimer et al., 2010	TRD	51.0	64.3	arTMS	10	100	N	50	1000	7.5	2	15	15000	12	0.500
Kong et al., 2023	MDD	24.0	25.0	iTBS	–	120	Y	120°	600	2	14	28	16800	32	0.780
Loo et al., 2007	TRD	49.8	47.4	arTMS	10	110	N	120	1500	2	10	20	30000	18	0.333
McGirr et al., 2015	TRD	47.7	25.0	arTMS	10	120	N	60	3000	2	10	20	60000	27	0.556
Modirrousta et al., 2018	MDD	45.4	47.0	arTMS	10	110	N	15	3000	2	15	30	90000	17	0.824
Quinn et al., 2023	MDD	65.0	12.0	iTBS	–	120	Y	50	1800	5	9	45	81000	25	0.520
Schulze et al., 2018	MDD/BD	39.7	24.6	arTMS	20	120	N	80	3000	2	10	20	60000	65	0.415
Wang et al., 2022	TRD	46.0	58.0	arTMS	15	110	N	60	3000	5	5	25	75000	31	0.645
Williams et al., 2018	MDD/BD	56.0	33.3	iTBS	–	120	Y	50	1800	10	5	50	90000	6	0.833
Zhang et al., 2024	MDD	14.8	90.3	iTBS	–	100	Y	10	600	2	10	20	12000	31	0.194
Zhao et al., 2024	TRD	18.6	27.3	iTBS	–	100	Y	50	1800	10	5	50	90000	20	0.650

Note. *from 15 to 20 min, **from 15 to 30 min; £from 120 to 360 min; #from 480 to 640 min; °minimum 120. Only interventions targeting the PFC were included; all but one targeted the DLPFC, with one targeting the DMPFC (i.e. Schulze et al., 2018). *Abbreviation.* arTMS: accelerated repetitive Transcranial Magnetic Stimulation; BD: Bipolar Disorder; iTBS: Intermittent Theta Burst Stimulation; MDD: Major Depressive Disorder; MT: Motor Threshold; RR: Response Rate (depression); TRD: Treatment-Resistant Depression; DLPFC: dorsolateral prefrontal cortex, DMPFC: dorsomedial prefrontal cortex.

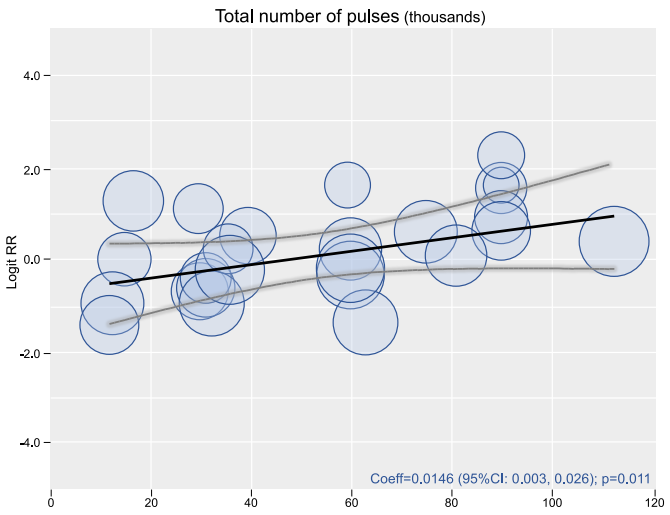

Fig. 1. Bubble plots with fitted meta-regression line (black) and 95 % CI (grey) showing the logit depression response rate against the total number of pulses (thousands) (n = 25 studies). R^2 (percentage of variance explained by the parameters): 11 %. Bubble sizes are proportional to the study weights. RR=Response Rate.

intervals are maintained. Specifically, intervals of at least 50 min appear to significantly enhance treatment efficacy (Cole et al., 2024). These results align with the principles of spaced learning, which posit that temporally distributed stimulation promotes synaptic consolidation and memory retention more effectively than massed training (Smolen et al., 2016). Consolidation theory suggests that synaptic plasticity is maximized when a subsequent trial follows the decay of the effects induced by the first. A refractory period has been proposed, during which premature stimulation fails to elicit additional potentiation. Mechanisms hypothesized to underlie this time-dependent LTP consolidation include priming and the activation of transcriptional processes. Although based on a meta-regression framework, our analysis provides preliminary clinical evidence consistent with laboratory findings that an inter-stimulation interval of approximately 40–50 min optimally enhances LTP via successive theta-burst stimulations, whereas shorter intervals lack additive effects (Kramár et al., 2012; Lynch et al., 2013). In the context of neuromodulation, appropriately spaced sessions may therefore optimize plasticity-related processes and contribute to more durable clinical outcomes.

In conclusion, this study provides valuable insights that may guide the development of more effective accelerated excitatory neuromodulation protocols. The analysis presents several limitations, stemming both from the inclusion of controlled and uncontrolled studies—which introduces methodological heterogeneity—and from the observational nature of meta-regression, which precludes causal inference. Furthermore, the results cannot be generalized to all intervention types, as the efficacy of inhibitory protocols may be influenced by distinct factors. Nonetheless, the number of sessions and intersession intervals have preliminarily emerged as key determinants of treatment outcomes, whereas the clinical relevance of targeting precision (e.g.,

Table 2
Main result for Model 1 (*dosing factor*)[£] (25 interventions; R^2 = 11 %).

Covariate	Coefficient	SE	95 % CI Lower	95 % CI Upper	Z value	p-value[#]
Intercept	−0.4679	0.3910	−1.2342	0.2984	−1.20	0.2314
TMS type: arTMS	−0.0333	0.6441	−1.2958	1.2292	−0.05	0.9587
Neuronavigation: No	−0.3449	0.6479	−1.6147	0.9249	−0.53	0.5945
Total pulses (thousands)	0.0146	0.0057	0.0034	0.0258	2.56	0.0106

Notes. [£]Random effects (MM), Z-distribution, Logit Response rate; [#]2-sided p-values. *Abbreviations*. arTMS: accelerated repetitive Transcranial Magnetic Stimulation; CI: Confidence interval; SE: standard error.

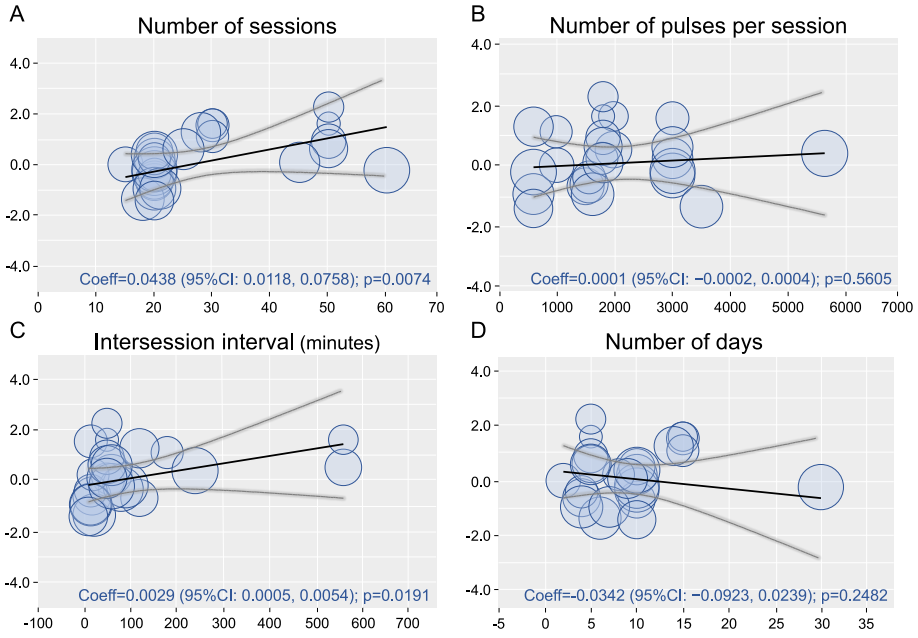

Fig. 2. Bubble plots with fitted meta-regression lines (black) and 95 % CIs (grey) showing the logit depression response rate against moderators: **a)** total sessions, **b)** pulses per session, **c)** intersession interval, **d)** days of treatment (n = 25 studies). R^2 (percentage of variance explained by the parameters): 20 %. Bubble sizes are proportional to the study weights. RR=Response Rate.

neuronavigation) may have been overemphasized. If confirmed by future research, these findings could play a crucial role in the optimization of arTMS protocols, ultimately increasing their efficacy in the treatment of clinical depression.

CRediT authorship contribution statement

Mauro Pettorruso: Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Marta Borgi:** Writing – original draft, Visualization, Formal analysis, Data curation. **Lorenzo Pio Padula:** Writing – review & editing, Formal analysis, Data curation. **Andrea Miuli:** Writing – review & editing, Data curation. **Beatrice Benatti:** Writing – review & editing, Visualization. **Roberto Guidotti:** Writing – review & editing, Data curation. **Laura Marzetti:** Writing – review & editing, Conceptualization. **Chris Baeken:** Writing – review & editing, Supervision. **Bernardo Dell'Osso:** Writing – review & editing, Conceptualization. **Giorgio Di Lorenzo:** Writing – review & editing, Conceptualization. **Francesca Zoratto:** Writing – original draft, Funding acquisition, Formal analysis, Data curation. **Giovanni Martinotti:** Writing – review & editing, Supervision.

Declaration of competing interest

Authors have nothing to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2025.10.043.

References

studies included in the meta-regression

* Baeken, C., Vanderhasselt, M.A., Remue, J., et al., 2013. Intensive HF-rTMS treatment in refractory medication-resistant unipolar depressed patients. J. Affect. Disord. 151 (2), 625–631. https://doi.org/10.1016/j.jad.2013.07.008.
* Barnes, R., Skvarc, D., Fitzgerald, P.B., et al., 2023. Equal remission rates and reduced length of hospital stay with twice-daily repetitive transcranial magnetic stimulation (rTMS) for major depression – a large naturalistic retrospective cohort association study. Prog. Neuropsychopharmacol. Biol. Psychiatry 127. https://doi.org/10.1016/j.pnpbp.2023.110820.
* Blumberger, D.M., Vila-Rodriguez, F., Wang, W., et al., 2021. A randomized sham controlled comparison of once vs twice-daily intermittent theta burst stimulation in depression: a Canadian rTMS treatment and biomarker network in depression (CARTBIND) study. Brain Stimul. 14 (6), 1447–1455. https://doi.org/10.1016/j.brs.2021.09.003.

Briley, P.M., Webster, L., Lankappa, S., Pszczolkowski, S., McAllister-Williams, R.H., Liddle, P.F., Auer, D.P., Morriss, R., 2024. Trajectories of improvement with repetitive transcranial magnetic stimulation for treatment-resistant major depression in the BRIGhTMIND trial. Npj Ment. Health. Res. 3 (1), 32. https://doi.org/10.1038/s44184-024-00077-8.

* Bröcker, E., van den Heuvel, L., Seedat, S., 2019. Accelerated theta-burst repetitive transcranial magnetic stimulation for depression in South Africa. S. Afr. J. Psychiatr. 25. https://doi.org/10.4102/sajpsychiatry.v25i0.1346.
* Bulteau, S., Beynel, L., Marendaz, C., et al., 2019. Twice-daily neuronavigated intermittent theta burst stimulation for bipolar depression: a randomized sham-controlled pilot study. Neurophysiol. Clin. 49 (5), 371–375. https://doi.org/10.1016/j.neucli.2019.10.002.

Caulfield, K.A., Fleischmann, H.H., George, M.S., McTeague, L.M., 2022. A transdiagnostic review of safety, efficacy, and parameter space in accelerated transcranial magnetic stimulation. J. Psychiatr. Res. 152, 384–396. https://doi.org/10.1016/j.jpsychires.2022.06.038.

Chen, L., Klooster, D.C.W., Tik, M., Thomas, E.H.X., Downar, J., Fitzgerald, P.B., Williams, N.R., Baeken, C., 2023. Accelerated repetitive transcranial magnetic stimulation to treat major depression: the past, present, and future. Harv. Rev. Psychiatr. 31 (3), 142–161. https://doi.org/10.1097/HRP.0000000000000364.

Cole, E., O'Sullivan, S.J., Tik, M., Williams, N.R., 2024. Accelerated theta burst stimulation: safety, efficacy, and future advancements. Biol. Psychiatry 95 (6), 523–535. https://doi.org/10.1016/j.biopsych.2023.12.004.

* Cole, E.J., Phillips, A.L., Bentzley, B.S., et al., 2022. Stanford neuromodulation therapy (SNT): a double-blind randomized controlled trial. Am. J. Psychiatr. 179 (2), 132–141. https://doi.org/10.1176/APPI.AJP.2021.20101429.
* Cole, E.J., Stimpson, K.H., Bentzley, B.S., et al., 2020. Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression. Am. J. Psychiatr. 177 (8), 716–726. https://doi.org/10.1176/appi.ajp.2019.19070720.
* Dardenne, A., Baeken, C., Crunelle, C.L., Bervoets, C., Matthys, F., Herremans, S.C., 2018. Accelerated HF-rTMS in the elderly depressed: a feasibility study. Brain Stimul. 11 (1), 247–248. https://doi.org/10.1016/j.brs.2017.10.018.
* Desbeaumes Jodoin, V., Miron, J.P., Lespérance, P., 2019. Safety and efficacy of accelerated repetitive transcranial magnetic stimulation protocol in elderly depressed unipolar and bipolar patients. Am. J. Geriatr. Psychiatr. 27 (5), 548–558. https://doi.org/10.1016/j.jagp.2018.10.019.
* Duprat, R., Desmyter, S., Rudi, D.R., et al., 2016. Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: a fast road to remission?. J. Affect. Disord. 200, 6–14. https://doi.org/10.1016/j.jad.2016.04.015.

Elbau, I.G., Lynch, C.J., Downar, J., et al., 2023. Functional connectivity mapping for rTMS target selection in depression. Am. J. Psychiatr. 180 (3), 230–240. https://doi.org/10.1176/appi.ajp.20220306.

* Filipčić, I., Šimunović Filipčić, I., Sučić, S., et al., 2021. A pilot investigation of accelerated deep transcranial magnetic stimulation protocols in treatment-resistant depression. Eur. Arch. Psychiatr. Clin. Neurosci. 271 (1), 49–59. https://doi.org/10.1007/s00406-020-01141-y.
* Fitzgerald, P.B., Chen, L., Richardson, K., Daskalakis, Z.J., Hoy, K.E., 2020. A pilot investigation of an intensive theta burst stimulation protocol for patients with treatment resistant depression: short title: intensive TBS in depression. Brain Stimul. 13 (1), 137–144. https://doi.org/10.1016/j.brs.2019.08.013.
* Fitzgerald, P.B., Hoy, K.E., Elliot, D., Susan McQueen, R.N., Wambeek, L.E., Daskalakis, Z.J., 2018. Accelerated repetitive transcranial magnetic stimulation in the treatment of depression. Neuropsychopharmacology 43 (7), 1565–1572. https://doi.org/10.1038/s41386-018-0009-9.

Gama-Chonlon, L., Scanlan, J.M., Allen, R.M., 2022. Could bipolar depressed patients respond better to rTMS than unipolar depressed patients? A naturalistic, observational study. Psychiatry Res. 312, 114545. https://doi.org/10.1016/j.psychres.2022.114545.

* Holtzheimer, P.E., McDonald, W.M., Mufti, M., et al., 2010. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. Depress. Anxiety 27 (10), 960–963. https://doi.org/10.1002/da.20731.

Hsu, T.W., Yeh, T.C., Kao, Y.C., Thompson, T., Brunoni, A.R., Carvalho, A.F., Hsu, C.W., Tu, Y.K., Liang, C.S., 2024. The dose-effect relationship of six stimulation parameters with rTMS over left DLPFC on treatment-resistant depression: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 162, 105704. https://doi.org/10.1016/j.neubiorev.2024.105704.

* Kong, Y., Zhou, J., Zhao, M., et al., 2023. Non-inferiority of intermittent theta burst stimulation over the left V1 vs. classical target for depression: a randomized, double-blind trial. J. Affect. Disord. 343, 59–70. https://doi.org/10.1016/j.jad.2023.09.024.

Kramár, E.A., Babayan, A.H., Gavin, C.F., Cox, C.D., Jafari, M., Gall, C.M., Rumbaugh, G., Lynch, G., 2012. Synaptic evidence for the efficacy of spaced learning. Proc. Natl. Acad. Sci. U. S. A 109 (13), 5121–5126. https://doi.org/10.1073/pnas.1120700109.

Lefaucheur, J.P., Colzi, C., Hollander, E., Pampaloni, I., Van Ameringen, M., Baeken, C., Fusar-Poli, P., Arango, C., Fontenelle, L.F., Batail, J.M., Brunoni, A.R., Nicolini, H., Haffen, E., Soriano-Mas, C., Rodriguez, C.I., Dell'Osso, B.M., Vieta, E., Sauvaget, A., Szekely, D., Mayer-Linderberg, A., Denys, D., Stein, D.J., Drapier, D., Voon, V., Pallanti, S., 2025. Comparison between accelerated and standard or sham rTMS in the treatment of depression: a systematic review. Neurosci. Biobehav. Rev. 173, 106140. https://doi.org/10.1016/j.neubiorev.2025.106140.

Lisanby, S.H., 2024. Transcranial magnetic stimulation in psychiatry: historical reflections and future directions. Biol. Psychiatry 95 (6), 488–490. https://doi.org/10.1016/j.biopsych.2023.05.001.

* Loo, C.K., Mitchell, P.B., McFarquhar, T.F., Malhi, G.S., Sachdev, P.S., 2007. A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. Psychol. Med. 37 (3), 341–349. https://doi.org/10.1017/S0033291706009597.

Lynch, G., Kramár, E.A., Babayan, A.H., Rumbaugh, G., Gall, C.M., 2013. Differences between synaptic plasticity thresholds result in new timing rules for maximizing long-term potentiation. Neuropharmacology 64 (1), 27–36. https://doi.org/10.1016/j.neuropharm.2012.07.006.

Makkinayeri, S., Guidotti, R., Basti, A., Woolrich, M.W., Gohil, C., Pettorruso, M., Ermolova, M., Ilmoniemi, R.J., Ziemann, U., Romani, G.L., Pizzella, V., Marzetti, L., 2025. Investigating brain network dynamics in state-dependent stimulation: a concurrent electroencephalography and transcranial magnetic stimulation study using hidden Markov models. Brain Stimul. 18 (3), 800–809. https://doi.org/10.1016/j.brs.2025.03.020.

* McGirr, A., Van Den Eynde, F., Tovar-Perdomo, S., Fleck, M.P.A., Berlim, M.T., 2015. Effectiveness and acceptability of accelerated repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant major depressive disorder: an open label trial. J. Affect. Disord. 173, 216–220. https://doi.org/10.1016/j.jad.2014.10.068.

Millet, B., Harika-Germaneau, G., Maatoug, R., Naudet, F., Reymann, J.M., Turmel, V., Batail, J.M., Soulabaille, J., Jaafari, N., Drapier, D., 2025. Repetitive Transcranial Magnetic Stimulation targeted with MRI based neuro-navigation in major depressive episode: a double-blind, multicenter randomized controlled trial. PLoS One 20 (5), e0317597. https://doi.org/10.1371/journal.pone.0317597.

* Modirrousta, M., Meek, B.P., Wikstrom, S.L., 2018. Efficacy of twice-daily vs once-daily sessions of repetitive transcranial magnetic stimulation in the treatment of major depressive disorder: a retrospective study. Neuropsychiatric Dis. Treat. 14, 309–316. https://doi.org/10.2147/NDT.S151841.

Pettorruso, M., d'Andrea, G., Di Carlo, F., De Risio, L., Zoratto, F., Miuli, A., Benatti, B., Vismara, M., Pompili, E., Nicolò, G., Niolu, C., Siracusano, A., Sensi, S.S., Dell'Osso, B., Di Lorenzo, G., Martinotti, G., ReModula Study Group, 2023. Comparing fast-acting interventions for treatment-resistant depression: an explorative study of accelerated HF-rTMS versus intranasal esketamine. Brain Stimul. 16 (4), 1041–1043. https://doi.org/10.1016/j.brs.2023.06.003.

* Quinn, D.K., Upston, J., Jones, T.R., et al., 2023. Electric field distribution predicts efficacy of accelerated intermittent theta burst stimulation for late-life depression. Front. Psychiatr. 14. https://doi.org/10.3389/fpsyt.2023.1215093.

Sack, A.T., Paneva, J., Küthe, T., Dijkstra, E., Zwienenberg, L., Arns, M., Schuhmann, T., 2024. Target engagement and brain state dependence of transcranial magnetic stimulation: implications for clinical practice. Biol. Psychiatry 95 (6), 536–544. https://doi.org/10.1016/j.biopsych.2023.09.011.

* Schulze, L., Feffer, K., Lozano, C., et al., 2018. Number of pulses or number of sessions? An open-label study of trajectories of improvement for once-vs. Twice-daily dorsomedial prefrontal rTMS in major depression. Brain Stimul. 11 (2), 327–336. https://doi.org/10.1016/j.brs.2017.11.002.

Shi, R., Wang, Z., Yang, D., Hu, Y., Zhang, Z., Lan, D., Su, Y., Wang, Y., 2024. Short-term and long-term efficacy of accelerated transcranial magnetic stimulation for depression: a systematic review and meta-analysis. BMC Psychiatry 24 (1), 109. https://doi.org/10.1186/s12888-024-05545-1.

Smolen, P., Zhang, Y., Byrne, J.H., 2016. The right time to learn: mechanisms and optimization of spaced learning. Nat. Rev. Neurosci. 17 (2), 77–88. https://doi.org/10.1038/nrn.2015.18.

Sterne, J.A.C., Savović, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., Cates, C. J., Cheng, H.Y., Corbett, M.S., Eldridge, S.M., Emberson, J.R., Hernán, M.A., Hopewell, S., Hróbjartsson, A., Junqueira, D.R., Jüni, P., Kirkham, J.J., Lasserson, T., Li, T., McAleenan, A., Reeves, B.C., Shepperd, S., Shrier, I., Stewart, L.A., Tilling, K., White, I.R., Whiting, P.F., Higgins, J.P.T., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. Br. Med. J. 366, l4898. https://doi.org/10.1136/bmj.l4898.

* Wang, Q., Huang, H., Li, D., et al., 2022. Intensive rTMS for treatment-resistant depression patients with suicidal ideation: an open-label study. Asian J. Psychiatr. 74. https://doi.org/10.1016/j.ajp.2022.103189.

* Williams, N.R., Sudheimer, K.D., Bentzley, B.S., et al., 2018. High-dose spaced theta-burst TMS as a rapid-acting antidepressant in highly refractory depression. Brain 141 (3), e18. https://doi.org/10.1093/brain/awx379.

Yu, C.L., Kao, Y.C., Thompson, T., Brunoni, A.R., Hsu, C.W., Carvalho, A.F., Chu, C.S., Tseng, P.T., Tu, Y.K., Yang, F.C., Su, K.P., Cheng, S.L., Hsu, T.W., Liang, C.S., 2024. The association of total pulses with the efficacy of repetitive transcranial magnetic stimulation for treatment-resistant major depression: a dose-response meta-analysis. Asian J. Psychiatr. 92, 103891. https://doi.org/10.1016/j.ajp.2023.103891.

* Zhang, M., Li, W., Ye, Y., Hu, Z., Zhou, Y., Ning, Y., 2024. Efficacy and safety of intermittent theta burst stimulation on adolescents and young adults with major depressive disorder: a randomized, double blinded, controlled trial. J. Affect. Disord. 350, 214–221. https://doi.org/10.1016/j.jad.2024.01.025.

* Zhao, H., Jiang, C., Zhao, M., et al., 2024. Comparisons of accelerated continuous and intermittent theta burst stimulation for treatment-resistant depression and suicidal ideation. Biol. Psychiatry 96 (1), 26–33. https://doi.org/10.1016/j.biopsych.2023.12.013.